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DRINKER BIDDLE & REATH (DC)
1500 K STREET, N.W.
SUITE 1100
WASHINGTON, DC 20005-1209

EXAMINER	
SLOBODYANSKY, ELIZABETH	
ART UNIT	**PAPER NUMBER**
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/402,093	OHSUYE ET AL.	
	Examiner	Art Unit	
	Elizabeth Slobodyansky, PhD	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007 & 27 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-73,76 and 78-98* is/are pending in the application.

4a) Of the above claim(s) *78,80,81 and 84-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54-73,76,79 and 94-98* is/are rejected.

7)☒ Claim(s) *82 and 83* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed in non-compliant form on January 16, 2007 and in compliant form on February 27, 2007 amending the specification to correct typographical errors, amending claims 54, 63-65, 69-72, 96 and 97, canceling claims 74, 75 and 77 and adding claim 98 has been entered.

Claims 54-73, 76 and 78-98 are pending. Claims 78, 80, 81 and 84-93 have been previously withdrawn.

Election/Restrictions

It is noted that Applicants previously elected the species of the fusion protein of SEQ ID NO:20 (May 19, 2006) and the peptide of interest of SEQ ID NO:27 (November 8, 2005). It is further noted that in the fusion protein of SEQ ID NO: 20 (GP97ompPR) "amino acids 1-110 comprise the protective peptide, amino acids 111-123 comprise the helper peptide" (Applicants' Remarks of May 19, 2006, page 5). Residues 124-154 correspond to SEQ ID NO:28 that comprises SEQ ID NO:27 (Figure 7). This election of SEQ ID NO:20 and 27 is carried over.

Drawings

The drawings were received on January 16, 2007 (Figure 24 A, B). These drawings are acceptable.

Specification

The Sequence Listing filed May 19, 2006 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

Both SEQ ID NO:22 and SEQ ID NO:23 are different from SEQ ID NOs: 22-23 shown at Figures 12 and 13, respectively, and in the Sequence Listing filed September 29, 1999. SEQ ID NO: 22 is now identical to SEQ ID NO:23. Both sequence have Glu instead of Gly at position 144. Furthermore, SEQ ID NO:23 has Lys instead of Pro at position 152.

Appropriate correction is required.

The disclosure is objected to because of the following: in the description of Figure 24 "NaCl" is mistyped at the 1st occurrence as amended on 1/16/07 and remains mistyped at the 2nd occurrence (substitute specification filed July 5, 2005, page 9).

Appropriate correction is required.

Claim Objections

Claims 63 and 69 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 63 reads "The process according to claim 54, wherein said peptide of interest has insulinotropic activity". The peptides of interest recited in claim 54 are GLP-1 derivatives that inherently have insulinotropic activity. Similarly, for claim 68.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 97 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim has been amended to recite SEQ ID NOs: 20, 21, 22 and 23. At least sequences of SEQ ID NOs: 22-23, as available in the latest paper copy and CRF, are different from the sequencers presented at the time the application was filed, *supra*.

Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

While no art was found for SEQ ID NO:20, the search of SEQ ID NOs:21-23 was not performed for the reasons discussed above.

Claims 54-73, 76, 79, 94-96 and 98 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 54-73, 76, 79, 94-96 and 98 are drawn to a process of making a peptide of interest using a cell transformed with an expression vector comprising a DNA encoding a protective peptide, a helper peptide and a peptide of interest, a vector and a cell comprising said DNA.

In view of the amendment of 1/16/07 limiting the peptide of interest to a specific glucagons-like peptide-1 (GLP-1) derivative, the previous rejection is withdrawn with regard to the genus of the peptides of interest but reinstated with regard to the genus of protective peptide and the genus of helper peptides. The representative species of said genera are limited to the protective and helper peptides that are part of SEQ ID NOs: 20-23. The specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding a protective or helper peptide and fails to provide any structure: function correlation present in all members of the claimed genus. The specification does not teach the production of any other peptide of interest. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of the species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude

that the applicant had possession of the claimed invention at the time the instant application was filed.

Claims 54-73, 76, 79, 94-96 and 98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process of making derivatives of human GLP-1 using fusion proteins shown at Figures 7, 11-13 (SEQ ID NOs: 20-23), does not reasonably provide enablement for a process of making a peptide of interest of SEQ ID NOs: 27-70 or any other GLP-1 derivative recited in the claims using other helper and protective peptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 54-73, 76, 79, 94-96 and 98 are directed to a process of making a peptide of interest using a cell transformed with an expression vector comprising a DNA encoding a protective peptide, a helper peptide and a specific peptide of interest, a vector and a cell comprising said DNA.

Therefore, they are drawn to a method of making of a genus of polypeptides of interest having the specific defined structures, wherein the isoelectric point of said peptide of interest connected to a helper peptide of any structure is between 8 and 12. While the specification teaches a method of making of a highly purified GLP-1 derivative using the specific construct comprising the specific helper peptide, it does not provide any guidance as to a process for producing a highly purified GLP-1 derivative using a helper peptide of an unknown structure. This would involve designing a helper peptide-

peptide of interest fusion with the only limitation of having isoelectric point in the wide range of 8-12. Therefore, the breadth of these claims is much larger than the scope enabled by the specification.

The claimed method encompasses purification of any peptide using a fusion of a peptide of interest and a helper peptide wherein the attachment of a helper peptide would change characteristics of the peptide of interest. This would involve experimentation to find the helper peptide that being attached to the peptide of interest would change characteristics of the latter, so that it would become possible to use the fusion of protective peptide, helper peptide and peptide of interest in a claimed method.

The state of the art is such that it is unpredictable which helper peptides other than the ones present in fusion proteins of SEQ ID NOs: 20-23 should be used. The specification provides no guidance on the matter.

It is known in the art that the relationship between the sequence of a polypeptide and its properties and tertiary structure is neither well understood nor predictable. Consequently, excessive trial and error experimentation would be required to identify the necessary helper sequence that would impart the properties allowing the production of a highly purified peptide of interest since the amino acid sequence of such a helper peptide useful with any peptide of interest could not be predicted *a priori*. The specification provides no guidance on predicting a helper of what structure would be suitable for a given peptide of interest. Furthermore, the development of an appropriate purification scheme for a peptide with known characteristics requires additional trial and error experimentation.

Therefore, one skilled in the art would require guidance as to how to make a highly purified peptide of SEQ ID NOs: 27-70 or other GLP-1 derivative recited in the claims using a helper peptide of any function and structure by a claimed process. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 54-73, 76, 79 and 94-98 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54-77, 79, 94-96 and 98 are amended to recite the peptide of interest of SEQ ID NOs: 27-70 or GLP-1 derivative. The claims are confusing because SEQ ID NOs: 27-70 are the sequences of GLP-1 derivatives that thus are recited twice. The claims should be amended to recite SEQ ID NO: after each specific GLP-1 derivative. For example, GLP-1 (7-36) (SEQ ID NO:27), GLP-1 (7-37) (SEQ ID NO:28), etc.

Claim 97 is confusing because at least SEQ ID NOs: 22-23 are different in the Sequence listing and at Figures 12-13.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 72, 73 and 76 are rejected under 35 U.S.C. 102(e) as being anticipated by Suzuki et al.

Suzuki et al. (US Patent 5,891,671) teach an expression vector comprising a DNA encoding a fusion protein comprising the protective peptide, helper peptide and 7-37 GLP-1 and an *E. coli* transformed with said vector (columns 5 and 6, columns 17-20, Examples 11-14, claim 13). Said protective peptide is a fragment of *E. coli* β-galactosidase that is used in the instant invention and cleavage site between a linker peptide and a peptide of interest is a Kex2 protease cleavage site as in the instant invention. The bond between protective and linker peptides represents another cleavage site.

Absent evidence to the contrary the fusion of the helper peptide and the 7-37 GLP-1 fusion has the requisite pI. They further teach other peptides of interest such as GLP-1 (7-36) NH_2 that can be obtained similarly (e.g., column 5, line 22).

The applied reference has a common inventor, Yuji Suzuki, with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Allowable Subject Matter

Claims 82 and 83 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Arguments

Applicant's arguments filed January 16, 2007 have been fully considered but they are not persuasive.

With regard to the 112, 1st paragraph written description rejection, Applicants argue that the rejection is overcome in view of amending the claims to recite GLP-1

derivatives (Remarks, p.14). This is not persuasive because the rejection was also over the genus of helper and protective peptides. This part of the rejection remains.

With regard to the 112, 1st paragraph enablement rejection, Applicants argue that it is overcome in view of the amendment reciting GLP-1 derivatives. This is not persuasive because the issue remains with helper and protective peptides other than used in the fusion proteins of SEQ ID NOs: 20-23.

The outstanding 112, 2nd paragraph rejection of claim 97 is withdrawn in view of the amendment. However, new 112, 2nd paragraph rejection of claim 97 and other claims is made.

With regard of the 102(e) rejection, Applicants argue that "The '671 patent does not teach or suggest the GLP-1 derivatives recited in claims 54 and 72 as amended. Additionally, claims 54-71 and 79, and 94-97 are directed to a process. This process uses two processing points. The '671 patent does not teach processing points, only one. Instead the '671 patent is characterized by the use of base rich region (such as His) in a linker peptide to enhance the action of a processing enzyme (Kex2)" (page 15). This is not persuasive with regard to the GLP-1 derivatives. Among the peptides of interest '671 patent teaches several peptides recited in the instant claims such as GLP-1 (7-37) and GLP-1 (7-36) NH_2, for example, (e.g., column 5, lines 21-22). With regard to the linker peptide, i.e. helper peptide, the rejected claims are not limited to the specific helper peptide or a specific cleavage site between the protective and helper peptides.

The arguments are persuasive with regard to the process claims. Therefore, the 102(e) rejection of the process claims is withdrawn.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky, PhD whose telephone number is 571-272-0941. The examiner can normally be reached on M-F 10:00 - 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, PhD can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

E. Slobodyansky

Elizabeth Slobodyansky, PhD
Primary Examiner
Art Unit 1652

May 24, 2007